

Neurocognitive interventions based on network neuroscience may break the cycle of drug addiction relapse

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ABSTRACT: In Malaysia, abstinence-centric programs failed to reduce drug use and stem the spread of HIV. The Malaysian government shifted its focus to implement harm reduction strategies with methadone maintenance therapy (MMT), in particular proving to be effective in improving the overall health and well-being of people who inject drugs (PWIDs). Despite this success, MMT retention rates remain low, as methadone is only able to stall drug consumption, but not stop it completely. Neuroimaging research revealed that PWIDs enrolled in MMT still display addictive behavior, including drug cue sensitivity, craving, and withdrawal, despite treatment adherence. Brain activity amongst treated PWIDs continues to bear similarities to untreated individuals, as they struggle with cognitive impairments and poor self-control. Findings from the emerging field of network neuroscience could provide fresh insight into the mechanics of addiction, especially the impact of substance abuse on brain-wide cognitive networks. Concurrently, the development of non-intrusive cognitive interventions, such as neurofeedback and transcranial magnetic stimulation, shows promise to reprogram a person's patterns of brain activity, including those regulated by large-scale networks, to a state resembling normalcy. We highlight the importance of relapse in the life-long rehabilitation of substance abuse. The lack of treatment options to handle relapse after successful harm-reduction policies is due to the absence of a conceptual framework to reason about interventions. We review recent research in the new field of network neuroscience, which suggests that altered brain activity due to drug addiction underlies the propensity for relapse and that this dysfunction is not addressed in drug rehabilitation programs. We hypothesize that non-invasive, non-pharmacological cognitive interventions based on network neuroscience to correct brain activity dysfunction associated with addiction are potential therapies to treat drug addiction relapse. In complement with medicine-substitution-based therapies, we hope this approach will finally break the cycle of addiction.

Keywords: addiction relapse; network neuroscience; cognitive intervention; pharmacological substitution therapy; drug addiction

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1.0 BACKGROUND

Malaysia's approach to drug addict rehabilitation shifted in 2005 from a policy of total abstinence in controlled environments towards a harm reduction

approach ([Vicknasingam and Mahmud, 2008](#)) to stem the burgeoning HIV epidemic in the country as people who inject drugs (PWID) comprise 66% of all HIV cases in Malaysia ([Ali et al., 2018](#)). The Harm Reduction

program comprising of needle syringe and exchange program (NESP), condom distribution, and methadone maintenance therapy (MMT), was initially carried out by non-governmental organizations, medical practitioners and was shown to avert HIV infections effectively. The program has been expanded significantly to include deployment at the National Anti-Drug Agency (NADA) and prison levels ([Naning et al., 2014](#)). MMT has demonstrated efficacy at reducing both heroin consumption and associated risky behaviors ([Wegman et al., 2017](#)). The Malaysian Methadone Treatment Outcome cross-sectional study involving 3254 respondents from 103 treatment centers in Malaysia established that MMT significantly improved reintegration of former-people who inject drugs (PWIDs) into normative living patterns, with 66% of patients working salaried jobs and experiencing an overall increased quality of life ([Ali et al., 2018](#)).

Since opiates are abused in 75% of drug-taking cases in Malaysia ([Chie et al., 2015](#)), MMT has significant potential to ameliorate the drug problem in Malaysia via rehabilitation. As a therapy, MMT is a corrective rather than curative, employing pharmacological substitution of opioids with methadone ([Baharom et al., 2012](#)) to relieve physical discomfort and pain arising from narcotic withdrawal and to block the euphoric effects of drugs ([Joseph et al., 2000](#)). However, long-term adherence to MMT, a key factor in the overall success of this therapy, is poor with a retention rate of ~20 to 60% in Malaysia ([Ramli et al., 2012](#); [Wickersham et al., 2013](#)) due to various socio-cultural-economic factors ([Mukherjee et al., 2016](#)). In Malaysia, the long-term economic sustainability of MMT programs is also questionable because public funds heavily subsidize methadone costs at RM58.2 million (USD 14.2 million) to treat 65,259 opioid dependents from 2006 to 2013 ([Naning et al., 2014](#)).

Notwithstanding the success at curtailing HIV spread, there is a lack of evidence that the drug rehabilitation programs successfully reintegrate former-PWIDs into society in a sustainable way. Early reports estimated drug relapse rates between 70 - 90% within the first year of rehabilitation ([Mazlan et al., 2006](#)) with 20 - 40% of PWIDs seeking rehabilitation at NADA Cure & Care Centres between 2013-2017 were registered, relapsed users ([Statistics of Drug Addicts by Case Studies, National Anti-drug Agency, Ministry of Home Affairs Malaysia](#)). Worldwide, there is emerging evidence that MMT only delays addictive drug-taking behavior in a dose-dependent manner ([Donny et al., 2002](#); [Wickersham et al., 2013](#)) but does not significantly

reduce incidents of relapse back into chronic drug use ([Clark et al., 2014](#)). Studies of rehabilitating PWIDs enrolled in MMT programs reported increased drug craving just before regular methadone administration ([Ilgen et al., 2008](#)), the persistence of craving even after receiving stable doses ([Strasser et al., 2010](#)) and continued use of illicit substances to cope with the physical and psychological symptoms of withdrawal ([Naji et al., 2016](#)). At best, MMT acts as a temporary respite to deal with craving and withdrawal symptoms but does little in the way of returning a recovering addict to sustained cognitive and behavioral normalcy.

1.1 A transient solution: Neuroimaging evidence of methadone's limitations

Neuroimaging studies report that MMT prolongs drug dependence and maintains the addicted state of the brain even after the completion of an MMT rehabilitation program ([Ma et al., 2011](#)). The brain continues to be primed, retaining responsiveness to drug cues ([Langleben et al., 2008](#)) that reinforce the desire for, and dependence on opioids as inhibitory cognitive control is overridden ([Zhang et al., 2017](#)). MMT-enrolees struggle to accomplish mundane, non-drug-related tasks ([Marvel et al., 2012](#)), exhibiting impaired goal-directed behavior ([Li et al., 2015](#)), and consequently increased levels of frustration and stress, thus intensifying cravings ([Marvel et al., 2012](#)).

Brain activity measurements are taken just before MMT commencement and again after 12 months of treatment revealed no change in brain reward circuitry, behavioral control, and error occurrence, despite treatment adherence ([Ye et al., 2018](#)), as patterns of brain activity after methadone administration simply mirrors that of untreated heroin consumption ([Wang et al., 2016](#)). Drug-related cognitive and emotional impairments persist amongst drug users treated with MMT ([Marvel et al., 2012](#)), including enhanced drug-related memory processing, manifesting salient emotional responses to drugs ([Chang et al., 2016](#)) and dysfunctional valuations of drug cues. This aberrant processing elevates the importance of opioids over non-drug-related rewards and biases a PWIDs' decision-making towards drug-taking tendencies ([Gradin et al., 2014](#)).

Unable to disassociate from intrusive thoughts of opioids and consumption-related cues, drug users on MMT are at risk of relapse ([Li et al., 2018](#)). It appears that methadone does not alter the neurological basis of craving and addiction ([Tau et al., 2014](#)) but only displaces opioids as the object of dependence, sans

pleasure ([Ma et al., 2011](#)). Indeed, PWIDs undergoing MMT face the greatest risk of relapse at the end of a 24-hour inter-dose period ([Langleben et al., 2008](#)). Taking a longer view, studies featuring 6- and 12-month follow-up measurements in relapsed MMT patients revealed continued abnormal attentional responses to, and increased valuation of, rewards, impaired reward expectation, debilitated inhibitory control, and dysfunctional decision-making, compared to healthy controls ([Chang et al., 2016](#)). Methadone alone was not enough to offset the dysfunction to brain circuitry that had developed as a result of prior sustained opioid use.

1.2 Cognitive interventions from network neuroscience may complement MMT for efficacious rehabilitation

Methadone therapy has undisputed and demonstrable benefits from public health and socioeconomic standpoint as it effectively reduces HIV transmission, risk-taking behavior, self-reported criminal activities, and mortality while improving employment rates among opioid PWIDs ([Musa et al., 2012](#)). However, MMT alone does not nullify the sensation of craving and drug-linked impairment of cognitive function and reward valuation in the brain. New interventions must jointly complement methadone to make rehabilitation sustainable and prevent relapse. Solving this problem requires an understanding of how to reverse cravings and the overriding impulsive and compulsive decision to take drugs, which perpetuates the dependence of PWIDs on drugs.

Recent advances in network neuroscience provide novel insights into the reconfiguration of brain activity patterns that accompany chronic drug use, hinting at novel interventions to restore normative cognitive activity. Network neuroscience is an emerging discipline studying the relationship between patterns of coordinated neural activity in the brain with mental function ([Bassett and Sporns, 2017](#)), augmenting the brain disease model of addiction ([Volkow et al., 2016](#)) with new scientific concepts for analyzing the functional dimension accompanying the physiological and molecular changes induced by habitual drug-taking. Studies from neuroimaging measurements using functional Magnetic Resonance Imaging (fMRI) revealed unique patterns of coordinated blood-flow ([Fox and Raichle, 2007](#)) from a network of brain regions that correspond to various cognitive tasks such as executive behavioral control ([Seeley et al., 2007](#)) and reward valuation ([van den Bos and McClure, 2013](#)). Disruptions in integrity or abnormality activity in these networks of neural agents within the brain have been linked to

neuropsychiatric disorders, including addiction ([Wang et al., 2018](#)).

Introspective, attentional, and memory-based brain networks are subverted to focus on, and reinforce, the pleasurable effects of drug-taking ([Evans and Cahill, 2016](#)), with reduced activation occurring after drug consumption ([Sutherland et al., 2012](#)). However, in the absence of drugs, craving is triggered by drug-linked visual or sensory cues ([Ekhtiari et al., 2016](#)) that cause emotional distress. These cues are elevated to importance within the addicted brain as salient internal and external stimuli that need to be acted on for relief and suppression of craving ([Janes et al., 2015](#)). Concomitant to greater attention towards drug cues induced by accumulation of stressful mental states, the valuation-control (VC) network ([van den Bos and McClure, 2013](#)) becomes disproportionately activated ([Xie et al., 2014](#)). This elevates the value of opioids and encourages the pursuit of drugs ([Zou et al., 2015](#)) to the exclusion of other positive goal-directed behaviors ([Janes et al., 2015](#)). In healthy non-PWIDs, the valuation and control elements of the VC compete amongst themselves to maintain a balanced mindset. If impulsive behavioral choices are being considered, the control element exerts more influence to provide a measure of self-control. However, amongst non-treated heroin users, a bias towards heroin consumption and the almost complete suppression of the control element occurs, resulting in the impulsive, all-consuming drive for drugs ([Zhai et al., 2015](#)). Recovering PWIDs on methadone still display impaired self-control ([Wang et al., 2018](#)), suggesting that methadone is unable to assist in re-balancing the valuation-control network. Consequently, repeated craving-induced cyclical stimulations of emotional, attentional, and valuation networks will trigger memory networks to program habitual activation of these brain patterns, which then manifest as the urge to consume drugs during times of duress ([Belin et al., 2013](#)).

Here is an opportunity for new interventions, specifically addressing relapse in the rehabilitation of chronic drug dependents. The activation of brain attention and valuation networks in rehabilitating drug PWIDs might be reprogrammed to mute responsiveness to drug cues, thereby attenuating craving and the value of drugs perceived by the brain. MMT will still be an essential prerequisite to brain network activity reprogramming, as it can reduce emotional distress ([Teoh et al., 2016](#)), making the brain more amenable to neurocognitive reprogramming ([Rezapour et al., 2017](#)). We, therefore, advocate the joint implementation of

neurocognitive interventions in tandem with existing methadone replacement therapies in Malaysia to provide a more holistic treatment plan when restoring normal cognitive function and prevent relapse. Such therapies do not involve the use of pharmaceuticals, relying instead on a patient's cognitive processes to reprogram the brain and break away from opioid dependencies. Examples of cognitive therapies include neurofeedback, mindfulness, and transcranial stimulation.

- **Neurofeedback** reduces drug-seeking symptoms while increasing abstinence duration by training the mind and body to act more optimally via improvements to emotive, cognitive, physical, and behavioral experiences ([Dehghani-Arani et al., 2013](#)). This method has been reported to successfully reprogram large-scale brain networks ([Nicholson et al., 2018](#)).
- **Mindfulness** is the systematic training of attention and self-control ([Garland and Howard, 2018](#)) to reduce stress as well as improve attention, emotional regulation, and cognitive performance across large-scale networks ([Tang et al., 2017](#)). Here, patients are encouraged to attend any thoughts, feelings, or sensations, without attempting to interfere with these ideas ([Garland and Howard, 2018](#)).
- **Transcranial magnetic stimulation (TMS)** is the non-invasive delivery of electric field pulses to the brain ([Lazzaro et al., 2008](#)) to facilitate long- and short-term neuronal and behavioral effects ([Diana et al., 2017](#)). This mode of therapy has been reported to reduce cocaine craving in PWIDs ([Politi et al., 2008](#); [Rapinesi et al., 2016](#); [Shen et al., 2016](#)) and inhibitory control ([Bellamoli et al., 2014](#)), possibly via its effects on dopamine and glutamate systems in the brain ([Diana et al., 2017](#)).

1.3 Lack of MMT Efficacy in Amphetamine-type Stimulant Users

Amphetamine-type Stimulants (ATS) use is a growing problem in Malaysia ([McKetin et al., 2008](#); [United Nations Office on Drugs and Crimes, 2010](#)) due to the high degree of co-use amongst opioid injectors ([Chawarski et al., 2012](#); [Desrosiers et al., 2016](#)), with

more than 60% of Malaysian opioid users also reporting a lifetime history of ATS use ([Vicknasingam et al., 2010](#)). Such co-use practices are considered a key contributing factor in the rise in HIV-positive cases as well as other infectious diseases in the country ([Bachireddy et al., 2011](#); [Chawarski et al., 2012](#); [Choo et al., 2015](#)), a situation already occurring in Israel ([Bonny-Noach, 2019](#)). Unfortunately, MMTs are not designed to support the treatment of ATS users ([Zhang et al., 2015](#); [Noori et al., 2016](#)), with ATS-influenced disruptions to MMT programs reported in China ([Zhang et al., 2019](#)) and Romania ([Alexandrescu, 2017](#)). In fact, ATS use amongst Malaysian MMT participants may reduce the efficacy of the program as a means of rehabilitation ([Singh et al., 2013](#)). Thus far, there have been no reports of neurofeedback therapy on ATS users. However, initial research utilizing mindfulness- ([Magor-Blatch, 2013](#); [Magor-Blatch et al., 2014](#)) and TMS-based therapies ([Wu et al., 2018](#)) appear promising, reducing the addictive pull of ATS. However, too few studies highlighting the effects of neurocognitive therapies on ATS users.

2.0 HYPOTHESIS

Non-pharmacological neurocognitive intervention therapies may repattern brain functional network activity in rehabilitated drug users to treat the potential for relapse into addiction. In combination with medicine-substitution therapy, these therapies form a complete and sustainable treatment to rehabilitate drug addiction in a sustained manner in PWIDs, including users co-administering opioids and ATS.

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